

Surgically Curable and Incurable Scirrhoues Carcinomas of the Stomach

SHOICHI KINUGASA, MD,^{1*} SHUN'ICHI ABE, MD,¹ MITSUO TACHIBANA, MD,¹
HIROSHI YOSHIMURA, MD,¹ NAOMI MONDEN, MD,¹ DIPOK KUMAR DHAR, MD,¹
NAOFUMI NAGASUE, MD,¹ YOJI HARADA, MD,² AND SABURO NAGAOKA, MD²

¹Second Department of Surgery and the Department of Laboratory Medicine, Shimane Medical University, Izumo, Japan

²Central Clinical Laboratory, Shimane Medical University, Izumo, Japan

Background and Objectives: The purpose of this study was to identify a subgroup of patients with scirrhoues carcinoma of the stomach who are more suitable for surgery by analysis of their clinicopathologic characteristics.

Methods: Seventy-three patients with scirrhoues gastric carcinoma who underwent gastrectomy between 1979 and 1994 were included in the study. Clinicopathological characteristics of 5-year survivors and nonsurvivors were compared. A multivariate analysis of various prognostic factors was performed.

Results: The 5-year survival rate was 31.4%; 78% (28/36) of nonsurvivors died of malignant ascites and only 8% (3/36) died of hepatic or lung metastasis. When clinicopathologic parameters of 5-year survivors and nonsurvivors were compared, age, tumor size, macroscopic appearance, pT, pN, pM, stage, peritoneal lavage cytology, residual tumor, extent of gastric resection, operation time, volume of blood loss, and transfusion were significantly different. By the multivariate analysis, residual tumor, pathological depth of tumor infiltration, blood transfusion, and histological type were the independent prognostic factors.

Conclusions: The prognosis of scirrhoues carcinoma of the stomach is mainly determined by the depth of penetration and curability. In order to obtain better survival, early detection of tumor while it is limited to T2 stage appeared most important. Aggressive surgery would be indicated for T3 tumors, but in the case of T4 tumors, extent of operation should be determined by other factors such as extent of nodal metastasis or presence of distant metastasis. *J. Surg. Oncol.* 1997;65:194–200. © 1997 Wiley-Liss, Inc.

KEY WORDS: prognosis; scirrhous; gastric cancer; surgery

INTRODUCTION

Despite the recent advances in the treatment of gastric carcinoma, surgical results of scirrhoues carcinoma of the stomach remain poor [1]. One of the reasons for the unsatisfactory outcome is the difficulty in detecting early stage disease. As most of the scirrhoues carcinomas grow insidiously, they are often detected as the type IV carcinoma of Borrmann's criteria [2] involving the entire stomach. The 5-year survival rate of such diseases ranges from 17.7% to 29.2% even after curative gastrectomy [3,4]. It is not infrequent, however, to see a patient with a hard tumor that is infiltrative but still completely re-

sectable. It has been suggested that earlier cancers with slightly depressed or flat morphology (type IIc or IIb by the description of Japanese Gastroenterological Endoscopic Society) are the precursor lesions of linitis plastica-type cancer [5]. In order to obtain therapeutic and biological insights, therefore, it should be more informative to consider this disease as a histological entity rather

*Correspondence to: Shoichi Kinugasa, MD, Second Department of Surgery, Shimane Medical University, 89-1 Enyacho, Izumo 693, Japan. Fax: 81-853-21-7329.

Accepted 12 April 1997

TABLE I. Scirrhouc Carcinoma of the Stomach*
A. Clinicopathologic Characteristics of the Two Groups of Patients

	Total (n = 73)	5-yr survivors (n = 19)	5-yr nonsurvivors (n = 49)	P
Age (yr)	28–87 (58.1 ± 13.6)	29–77 (51.8 ± 13.8)	28–87 (60.4 ± 13.0)	0.0189
Sex				0.9999
male	39	10	27	
female	34	9	22	
Location ^a				0.5093
proximal	22	6	14	
distal	26	5	19	
Maximum diameter (cm)	1.4–21.0 (9.8 ± 4.7)	1.4–15.5 (5.3 ± 3.3)	5.0–21.0 (11.5 ± 3.9)	<0.0001
Macroscopic appearance				<0.0001
ulcerative	14	11	1	
ulcerative and infiltrative	17	6	11	
diffusely infiltrative	42	2	37	
Histology				0.2783
tubular	6	0	6	
poorly differentiated	45	13	29	
signet cell ring	22	6	14	
pT				<0.0001
T2	13	12	0	
T3	38	6	28	
T4	22	1	21	
pN				0.0454
N0	13	7	5	
N1	22	5	16	
N2	38	7	28	
pM				0.0014
M0	49	18	26	
M1	24	1	23	
peritoneum	15	1	14	0.0505
lymph nodes	10	0	10	0.0516
Stage				<0.0001
Ia, Ib	8	7	0	
II	6	3	3	
IIIa, IIIb	32	8	20	
IV	27	1	26	
Peritoneal lavage cytology				0.0014
negative	50	19	30	
positive	21	0	18	
unknown	2	0	1	

*Excluding tumors occupying whole stomach or middle one region.

*Mean values ± standard deviations in parentheses.

(Continued)

than a condition defined by its macroscopic morphology. In this study, scirrhouc carcinoma was defined by its amount of interstitial connective tissue in the histological examination [6]. This study was intended to analyze clinico-pathologic features of scirrhouc carcinoma of the stomach in 78 patients in order to elucidate whether it is possible to identify a subgroup of patients who are more suitable for aggressive surgical intervention.

MATERIALS AND METHODS

Patients

Between November 1979 and May 1994, 693 patients with primary gastric adenocarcinoma underwent gastric

resection in our department. Among these, 78 cases were diagnosed as scirrhouc type carcinoma, which was defined by the amount of interstitium regardless of gross appearance or histology. Specifically, presence of >50% of stromal connective tissue, not only in the central but also in the peripheral or deepest portions of the tumor in the hematoxylin-eosin stained section, was the basis for inclusion, which was determined by two pathologists (Y.H. and S.N.). Those of medullary or mixed-type histology were excluded. Five of the 78 patients who died of other causes than progression of cancer were excluded from the analysis of prognostic factors. Staging was based on the TNM classification [7]. All deaths by the

TABLE I. Scirrhouc Carcinoma of the Stomach (Continued)
B. Clinicopathologic Characteristics of the Two Groups of Patients

	Total (n = 73)	5-yr survivors (n = 19)	5-yr nonsurvivors (n = 49)	<i>P</i>
Gastrectomy				0.0008
partial	22	12	9	
total	51	7	40	
Combined resection				0.0294
none	29	12	16	
performed	44	7	33	
spleen	41	7	30	0.1035
pancreas	20	0	18	0.0015
others	10	0	10	0.0516
Residual tumor				<0.0001
R0	39	19	18	
R1	13	0	11	
R2	21	0	20	
Chemotherapy				0.5542
no	4	0	3	
yes	69	19	46	
Operation time (min.)				
mean \pm SD	249.7 \pm 70.4	220.8 \pm 44.9	266.8 \pm 75.0	0.0031
range	150–480	150–300	150–480	
Blood loss (ml)				
mean \pm SD	703.1 \pm 484.4	443.4 \pm 224.0	842.2 \pm 516.9	<0.0001
range	70–2890	70–1064	150–2890	
Blood transfusion				
no	18	9	4	0.0007
yes	55	10	45	

recurrence of cancer occurred within 5 years postoperatively. Therefore, 19 patients who survived >5 years after operation were grouped as the 5-year survivors. Five patients who were alive, but operated on within 5 years were excluded. Forty-nine patients died of their residual cancer or recurrent diseases and were grouped as the 5-year nonsurvivors. Clinicopathologic features were compared between these two groups.

Statistics

Demographic figures of the two groups were compared by the Student's or Welch's *t*-test, Chi-square test, and exact Fisher's probability test, when appropriate. Survival rates were calculated by the Kaplan-Meier method, and the difference was analyzed by the log-rank test. *P* values of <0.05 were considered statistically significant. The prognostic factors were evaluated by the Cox's proportional hazard model with a log-linear risk function [8].

RESULTS

During the 16-year period reviewed, the incidence of scirrhouc gastric cancer by the criteria of this study was 11.3% (78/693) of the all resected patients. Five patients died of causes other than cancer (three postoperative complications, one cerebral infarction, and one hepatic failure from cirrhosis). Table 1A shows the clinicopath-

ologic characteristics of the 73 evaluable patients. The mean age of 58.1 years and the male-to-female ratio of 1.15 for these patients were significantly younger and less male-predominant compared with other nonscirrhouc gastric cancer patients operated on in our department (64.0 years, *P* < 0.01 and 2.12, *P* < 0.05, respectively). Macroscopically, not only diffusely infiltrative type tumors, but also ulcerative type (IIc or Borrmann type 2) and ulcerative-infiltrative type (Borrmann type 3) occurred frequently. Histologically, poorly differentiated adenocarcinoma and signet-ring cell carcinoma were most common, but six cases were of moderately differentiated tubular adenocarcinoma. The mean diameter of the lesion was 9.8 ± 4.7 cm. Although all tumors were advanced (pT \geq 2), 13 patients were without lymph node metastasis. Distant metastasis was present in 24 patients, in the form of peritoneal dissemination or distant nodal metastasis. Hematogenous metastasis to the liver was not observed.

Table 1B summarizes the therapeutic aspects of the study. Partial gastrectomy was performed in 22 patients and total gastrectomy in 51. Curative operation without macroscopic residual tumor was possible in 39 patients (53%). The mean blood loss was 703 ± 484 ml and blood transfusion was done in 55 patients. Excluding four patients who were in unsatisfactory condition, adjuvant

chemotherapy (Mitomycin C and fluorinated pyrimidines) was given in 69 patients postoperatively.

The comparison of the 5-year survivors and nonsurvivors is shown in Table 1. Survivors were younger and in less advanced stages than nonsurvivors. Less extensive operations in terms of the extent of gastric resection and the combined resection of other organs were performed in the survivors. Survival curves according to the stage, depth of the tumor, residual tumor, and histology are shown in Figures 1 and 2. Survival curves after curative operation according to macroscopic appearance are shown in Figure 3. Of the 11 clinicopathologic variables that influenced survival on univariate analysis, residual tumor, pathological depth of tumor infiltration, blood transfusion, and histological type were independently significant when analyzed by the multivariate method (Table II).

Twenty-one patients were alive during the follow-up, and 52 died of recurrence or progression of the disease. In 36 patients whose causes of death were known in detail, 28 (78%) died with ascites containing cytologically confirmed malignant cells. Liver metastases were recognized in three patients and lung metastases in one (Table III).

DISCUSSION

Borrmann type IV carcinoma or linitis plastica-type gastric cancer is considered to be an advanced state of scirrhus carcinoma. Nakamura et al. [5] proposed that slightly depressed lesions (type IIc) located in the fundus, without convergence of the mucosal folds, represented the early-stage feature of linitis plastica cancer. They also considered that Borrmann type IV carcinomas originating from the pyloric gland took the same morphology in their early development. In order to evaluate the prognostic factors and to define the role of surgical treatment, therefore, selection of the patients for the analysis of scirrhus gastric cancer should be based on the histological characteristics of the tumor, rather than macroscopic appearance of the advanced lesion.

In the present study, 14 ulcerative lesions (12 slightly depressed and 2 ulcerative localized lesions) were included. All of the 12 slightly depressed lesions were thought to be early cancers in the preoperative evaluation, but they unexpectedly infiltrated throughout the muscularis propria with vast interstitia. Hirayama et al. [9] reported that the poorly differentiated, penetrating-type gastric cancer was the initial lesion of linitis plastica-type cancer from its clinicopathologic characteristics and that epidermal growth factor and transforming growth factor-beta played an important role in its growth. Although most of the scirrhus carcinomas of this series were composed of poorly differentiated or signet ring cell carcinoma, six cases were of moderately differentiated tubular carcinoma. Macroscopically, they presented

as Borrmann type III and IV cancers (three cases each). Of particular interest was that all of them infiltrated through the serosa and all six died within 2 years (Fig. 2). The reason for this unfavorable prognosis of the tubular type tumors is unclear. It is possible that they grew like the usual tubular carcinoma in their early stages and then acquired scirrhus phenotype as the result of malignant evolution, enhancing the malignant potential of the original tumors.

In this series, total gastrectomy was the surgery most frequently performed, and radical resection of adjacent organs as often done. The reported 5-year survival rates of Borrmann type IV carcinomas after curative resection ranged from 17.7% to 29.2% [3,4]. In this study, the 5-year survival of Borrmann type IV carcinomas after curative resection (RO) was 11% [Fig. 3].

The indication for aggressive surgery for advanced gastric carcinoma is difficult to define. Furukawa et al. [11] employed left upper abdominal evisceration plus Appleby's method [10] in 30 cases of Borrmann type IV carcinomas. They concluded that this method was a rational and useful technique for the surgical treatment of stages II and III Borrmann IV carcinomas, the 3-year survival rate of which was 83% [11]. This operation, however, could not improve the survival of stage IV cancer compared with total gastrectomy with pancreaticosplenic resection (12% vs. 10%).

Aranha et al. [12] compared patients who underwent total gastrectomy with patients without gastrectomy and concluded that total gastrectomy for linitis plastica should be reserved for those patients who have diseases limited to the stomach or regional lymph nodes and that others should be offered alternative treatment. In the current study, depth of tumor infiltration emerged as one of the significant factors in multivariate analysis. All patients with T2 tumors survived >5 years. Of patients with T3 tumor, 24% survived for 5 years, but all except one with T4 tumors died within 5 years. This suggests that aggressive resection of the stomach should be reserved for tumors limited to T3 stage. As to the combined resection of other organs, most patients who underwent resection of adjacent structures other than spleen, i.e., pancreas, colon, or ovary, did not survive. In a rare instance, however, a 63-year-old female who underwent total gastrectomy and resection of pancreas, spleen, and peritoneal metastases to the omentum for stage IV (T4N2M1) cancer had survived 6 years until she was lost to follow-up.

In patients with T4 tumors, it would be appropriate to perform en bloc resection of the invaded organ with extended nodal dissection when nodal metastasis is limited and there is no distant spread. Otherwise, the operation should be kept to a minimum to remove only bleeding or obstructing tumors. In such cases, more emphasis should

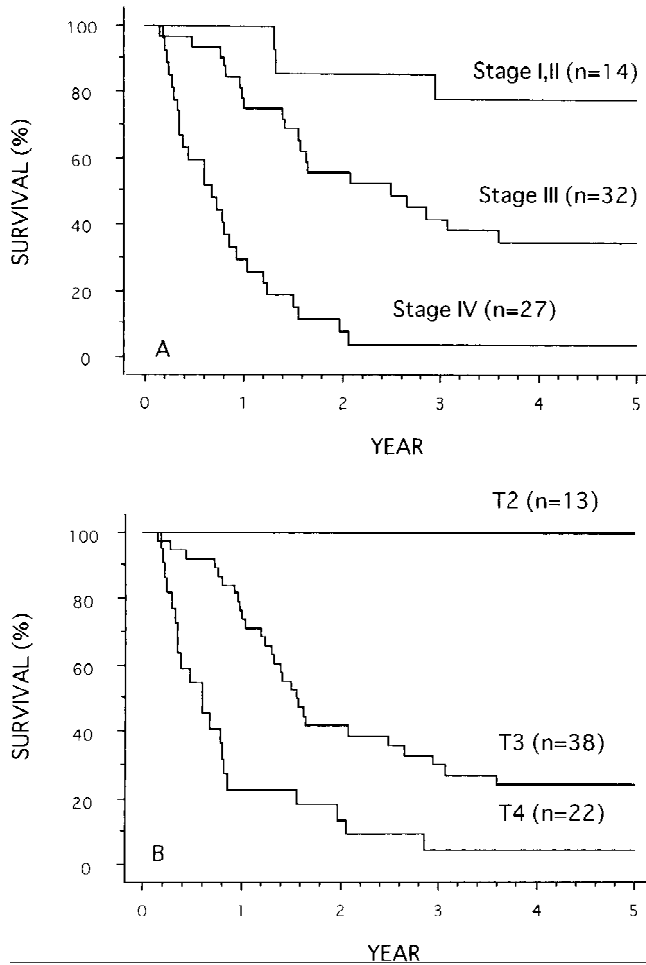


Fig. 1. **A:** The 5-year survival rate of stages I and II, stage III, and stage IV were 78%, 35%, and 4% ($P < 0.001$). **B:** The 5-year survival of tumor depth T2, T3, and T4 were 100%, 24%, and 5% ($P < 0.01$).

be placed on adjuvant therapy. The incidence of metastatic splenic hilar nodes in those who underwent splenectomy was similar in both 5-year survivors and non-survivors (2/7 vs. 11/30). In this study, the efficacy of splenic hilar lymph node dissection could not be shown with statistical significance. The morbidity, mainly left subphrenic abscess, was higher in patients with splenectomy than in those without splenectomy (15/41 vs. 4/32). However, in two of the seven survivors with positive splenic hilar nodes, it was possible to state that the performance of splenectomy saved these patients. Splenectomy should not be performed indiscriminately, but the specific indication and selection of patients are still unclear.

Some studies demonstrated the adverse influence of blood transfusion on the prognosis of patients with gastric cancer [13]. Others showed that it did not appear to have deleterious effects on the prognosis after stratifying the patients into stages [14]. Although blood transfusion was the third significant prognostic factor in the current

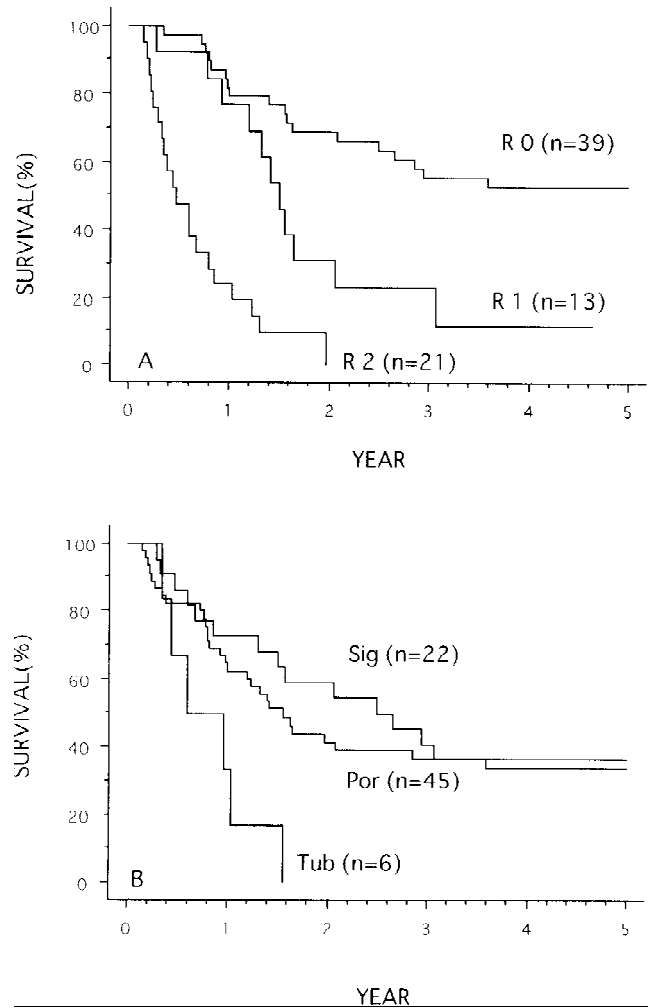


Fig. 2. **A:** The 5-year survival rate of residual tumor, R0, R1, and R2 were 53%, 12%, and 0% ($P < 0.001$). **B:** The 5-year survival of signet ring cell carcinoma (Sig), poorly differentiated adenocarcinoma (Por), and moderately differentiated adenocarcinoma (Tub), were 36%, 34%, and 0% ($P < 0.05$).

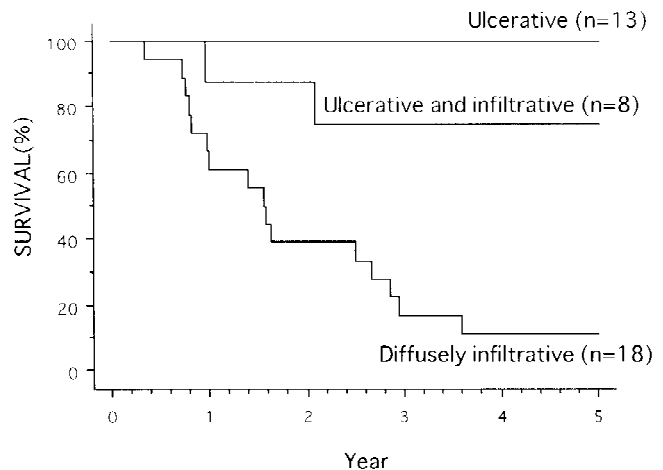


Fig. 3. The 5-year survival rate of ulcerative, ulcerative and infiltrative, and diffusely infiltrative tumors after curative operation were 100%, 75%, and 11% ($P < 0.01$).

TABLE II. Cox's Proportional Hazards Regression Model of Factors Affecting Survival of Patients With Scirrhus Carcinoma of the Stomach

	Univariate analysis		Multivariate analysis	
	Coefficient (s.e.)	P value	Coefficient (s.e.) ^a	P value
1. Residual tumor	1.187 (0.192)	<0.0001	0.911 (0.240)	0.0001
2. pT ^b	1.403 (0.233)	<0.0001	0.948 (0.334)	0.0046
3. Blood transfusion		0.0004		0.0118
no	-1.552 (0.437)		-1.279 (0.508)	
yes	—		—	
4. Histology		0.0246		0.0119
tubular	—		—	
poorly differentiated	-1.082 (0.461)		-0.020 (0.567)	
signet ring cell	-1.366 (0.507)		-1.145 (0.599)	

^aStandard error.

^bPathological depth of tumor infiltration.

TABLE III. Cause of Death in Patients With Scirrhus Gastric Cancer

Malignant ascites ^a	28
Malignant pleural effusion	3
Liver metastasis	2
Liver and lung metastasis	1
Remnant stomach cancer	1
Cachexia	1
Details unknown	16

^aThree of 28 patients died from malignant ascites accompanied by malignant pleural effusion.

study, the association of transfusion and tumor advancement remains as the possible explanation.

Regarding adjuvant therapy, mitomycin C (MMC) and antimetabolites were used in most of the patients in this series. Kurihara et al. [15] reported the results of questionnaires collected from 108 hospitals in Japan. The agents most frequently administered singly or in combination were 5-fluorouracil (5-FU), MMC, or tegafur. Recently, cisplatin has been used in combination with other drugs. Preusser et al. [16] reported the phase II study with the combination of etoposide, doxorubicin, and cisplatin for advanced gastric cancer, and in 43 out of 67 patients (64%), an objective response was achieved. Others [17] reported that the use of cisplatin produced better response and prolonged survival of scirrhus carcinoma. The actual impact of such therapy on patients' survival remains to be established.

In the current study, curability of the operation and the depth of tumor infiltration were the most important prognostic factors. Although lymph node metastasis was usually considered to be important [4,18], its prognostic significance appeared to be surmounted by the impact of the serosal penetration of the tumor in scirrhus gastric carcinoma. It is encouraging that the prognosis of histologically defined scirrhus cancer was favorable if it was removed before serosal encroachment occurred. Early detection is apparently the most effective means to

achieve longer survival, and the importance of careful endoscopic evaluation of patients with minimal complaints should be stressed.

REFERENCES

1. Kitamura K, Beppu R, Anai H, Ikejiri K, Yakabe S, Sugimachi K, Saku M: Clinicopathologic study of patients with Borrmann type IV gastric carcinoma. *J Surg Oncol* 1995;58:112-117.
2. Borrmann R: Geschwulste des Magens und Duodenums. In Henke F, Lubarsch O (eds): "Handbuch der speziellen pathologischen Anatomie und Histologie," Vol. IV/1. Berlin: Springer, 1926, p 812-1054.
3. Maehara Y, Moriguchi S, Orita H, Kakeji Y, Haraguchi M, Korenaga D, Sugimachi K: Lower survival rate for patients with carcinoma of the stomach of Borrmann type IV after gastric resection. *Surg Gynecol Obstet* 1992;175:13-16.
4. Arveux P, Faivre J, Boutron M-C, Piard F, Dusserre-Guion L, Monnet E, Hillon P: Prognosis of gastric carcinoma after curative surgery: A population-based study using multivariate crude and relative survival analysis. *Dig Dis Sci* 1992;37:757-763.
5. Nakamura K, Kato Y, Misono T, Sugano H, Sugiyama N, Baba Y, Maruyama M, Takagi K: Growing process to carcinoma of linitis plastica type of the stomach from cancer-development. I to Cho (Stomach and Intestine) 1980;15:225-234.
6. Japanese Research Society of Gastric Cancer: "The General Rules for the Gastric Cancer Study," 12th ed. Tokyo: Kanehara Shuppan, 1993.
7. Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ (eds): "Manual for Staging of Cancer," 4th ed. Philadelphia: J.B. Lippincott, 1992.
8. Kalbfleisch JD, Prentice RL: The proportional hazards model. In: Kalbfleisch JD, Prentice RL (eds): "The Statistical Analysis of Failure Time Data." New York: Wiley & Sons, 1980, p 84-92.
9. Hirayama D, Fujimori T, Satonaka K, Nakamura T, Kitazawa S, Horio M, Maeda S, Nagasako K: Immunohistochemical study of epidermal growth factor and transforming growth factor- β in the penetrating type of early gastric cancer. *Hum Pathol* 1992;23:681-685.
10. Appleby LH: The celiac axis in the expansion of the operation for gastric carcinoma. *Cancer* 1953;6:704-707.
11. Furukawa H, Hiratsuka M, Iwanaga T: A rational technique for surgical operation on Borrmann type 4 gastric carcinoma: Left upper abdominal evisceration plus Appleby's method. *Br J Surg* 1988;75:116-119.
12. Aranha GV, Georgen R: Gastric linitis plastica is not a surgical disease. *Surgery* 1989;106:758-763.
13. Sugezawa A, Kaibara N, Sumi K, Ohta M, Kimura O, Nishidoi H, Koga S: Blood transfusion and the prognosis of patients with gastric cancer. *J Surg Oncol* 1989;42:113-116.
14. Kampschoer GHM, Maruyama K, Sasako M, Kinoshita T, van de

- Velde CJH: The effects of blood transfusion on the prognosis of patients with gastric cancer. *World J Surg* 1989;13:637–643.
15. Kurihara M, Izumi T, Sasaki Y, Maruyama T, Miyasaka K: The chemotherapy of unresectable Borrmann type 4 gastric cancer. *Jpn J Cancer Chemother* 1983;10:2468–2477.
 16. Preusser P, Wilke H, Achterrath W, Fink U, Lenaz L, Heinicke A, Meyer J, Meyer HJ, Buente H: Phase II study with the combination etoposide, doxorubicin, and cisplatin in advanced measurable gastric cancer. *J Clin Oncol* 1989;7:1310–1317.
 17. Suga S, Kimura K, Nagai H, Kyogane K, Indoh M, Horizawa M, Suzuki N, Sugita Y, Matsuyama T, Maruyama K, Iwase H, Ina K, Horiuchi Y, Mitsuura T, Morise K, Saito H: An evaluation of gastric cancers given UFT/CDDP chemotherapy. *Jpn J Cancer Clin* 1991;37:929–939.
 18. Abe S, Yoshimura H, Tabara H, Tachibana M, Monden N, Nakamura T, Nagaoka S: Curative resection of gastric cancer: Limitation of peritoneal lavage cytology in predicting the outcome. *J Surg Oncol* 1995;59:226–229.